# The Effect of Exercise Timing on Glycemic Control: A Randomized Clinical Trial

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<sup>1</sup>Discipline of Exercise Science, Murdoch University, Perth, AUSTRALIA; <sup>2</sup>Faculty of Nutrition and Exercise Physiology, University of Missouri, Columbia, MO; <sup>3</sup>School of Human Sciences (Exercise and Sport Science), University of Western Australia, Perth, AUSTRALIA; and <sup>4</sup>Centre for Molecular Medicine & Innovative Therapeutics, Murdoch University, Perth, AUSTRALIA

#### ABSTRACT

TEO, S. Y. M., J. A. KANALEY, K. J. GUELFI, K. J. MARSTON, and T. J. FAIRCHILD. The Effect of Exercise Timing on Glycemic Control: A Randomized Clinical Trial. Med. Sci. Sports Exerc., Vol. 52, No. 2, pp. 323-334, 2020. Despite the acknowledgment of exercise as a cornerstone in the management of type 2 diabetes (T2D), the importance of exercise timing has only recently been considered. Purpose: This study sought to determine the effect of diurnal exercise timing on glycemic control in individuals enrolled in a 12-wk supervised multimodal exercise training program. A secondary aim was to determine the effect of diurnal exercise timing on the circadian rhythm of wrist skin temperature. Methods: Forty sedentary, overweight adults (mean  $\pm$  SD, age = 51  $\pm$  13 yr; body mass index = 30.9  $\pm$  4.2 kg m<sup>-2</sup>; women, n = 23) with and without (n = 20) T2D diagnosis were randomly allocated to either a morning (amEX) or an evening (pmEX) exercise training group. The supervised 12-wk (3 d·wk<sup>-1</sup>) program, comprised 30 min of moderate-intensity walking and 4 resistance-based exercises (3 sets, 12-18 repetitions each). Glycemic outcomes (glycated hemoglobin, fasting glucose, postprandial glucose) and wrist skin temperature were assessed at baseline and postintervention. Results: Exercise training improved (main effect of time, all P < 0.01) all glycemic outcomes; however, this was independent of allocation to either the amEX (Hedge's g, 0.23–0.90) or the pmEX (Hedge's g, 0.16–0.90) group. Accordingly, the adopted exercise training program did not alter the circadian rhythm of skin temperature. When only T2D individuals were compared, amEX demonstrated greater effects (all Hedge's g) on glycated hemoglobin (amEX, 0.57; pmEX, 0.32), fasting glucose (amEX, 0.91; pmEX, 0.53), and postprandial glucose (amEX, 1.12; pmEX, 0.71) but was not statistically different. Conclusions: Twelve weeks of multimodal exercise training improved glycemic control and postprandial glycemic responses in overweight non-T2D and T2D individuals. However, no distinct glycemic benefits or alterations in circadian rhythm were associated with morning versus evening exercise, when performed three times per week in this cohort. Key Words: DIURNAL TIMING, SECOND MEAL PHENOMENON, DAWN PHENOMENON, GLYCEMIC CONTROL, INSULIN SENSITIVITY

Performing exercise at least once per week can reduce the incidence of type 2 diabetes (T2D) in women (1) and men (2) and is an important adjunct in the management of blood glucose for individuals with existing T2D (3). Exercise—defined herein as planned, structured physical activity with the aim of increasing fitness—improves glycemic control via acute responses and chronic adaptations in local musculature (4) and in concert with systemic responses and adaptations in hepatic, neural, immune, endocrine, and metabolic factors (5). Each of these responses are in turn moderated

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by the intensity, duration, and type of exercise performed, as well as the frequency of exercise when performed within a training program (3,6). Beyond these established factors, the timing of exercise relative to meal ingestion has emerged as a factor potentially moderating the glycemic response to exercise (7,8), with postprandial exercise appearing to be most beneficial to improving glycemic control. Although the diurnal timing of exercise (i.e., morning vs evening) training has been shown to affect athletic performance, with enhanced an aerobic performance in the late afternoon (9), the role of diurnal exercise timing on glycemia or glycemic control has, to the best of our knowledge, not been directly assessed.

Glucose tolerance demonstrates a diurnal rhythm in healthy humans (10) with higher (improved) glucose tolerance in the morning than in the afternoon and evening (11). However, this rhythm in glucose tolerance is blunted in individuals with T2D, wherein glucose tolerance in the morning becomes similar to the afternoon (12). The observed diurnal rhythm in metabolic regulation along with the apparent disrupted rhythm in pathophysiological states has renewed interest in the association between the circadian system and the metabolic function (13–15).

The circadian system in humans is complex, comprising a network of cellular clocks that possess the ability to autonomously

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maintain a circadian rhythm (14,15). Despite their autonomous ability, the alignment of these clocks to external cues and each other (i.e., cellular clocks between tissues) is important (14,16), especially where multiple tissues and systems are involved in controlling the metabolic process (e.g., blood glucose concentration). Specifically, misalignment/disruption of these clocks may result in metabolic disturbance, whereas metabolic disturbance may in turn lead to misalignment in clocks (13,14). Exercise (physical activity) has been shown to be an important external cue capable of shifting the circadian rhythm (i.e., clock gene expression) in both the suprachiasmatic nucleus (central clock) of the hypothalamus (species: hamster [17]) and the skeletal muscle (species: mammals, including humans [13,15]) and, if consistently maintained, may entrain or align these clocks. Analysis of peripheral skin temperature is a useful marker of circadian rhythm in humans (18), and disruptions in skin temperature rhythm have been identified in individuals with T2D and metabolic syndrome (19,20).

The primary aim of this study therefore was to determine whether diurnal exercise timing, within the context of a 12-wk supervised multimodal exercise training program, differentially alters glycemic control in sedentary, overweight individuals both with and without T2D. Because the depletion of muscle glycogen increases insulin sensitivity and action (4) as well as glycogen synthase activity (21), and evening exercise is expected to result in a prolonged partial depletion of muscle glycogen overnight, we hypothesized evening exercise would result in greater improvements in glycemic control than exercise performed in the morning. A secondary aim of the study was to determine whether the diurnal timing of exercise performed 3 d·wk<sup>-1</sup> was sufficient to alter the circadian rhythm of skin temperature (18) and potentially explain improvements in glycemic control. We hypothesized that exercise training would result in skin temperature entrainment, as evidenced by divergent responses in the peripheral skin temperature rhythm of individuals enrolled in either the morning or the evening exercise training groups.

## **METHODS**

Using a parallel study design, participants were randomly allocated into 12-wk multimodal exercise training intervention performed either in the morning (amEX) or in the evening (pmEX). The study was approved by Murdoch University Human Research Ethics Committee, Western Australia, and written informed consent was obtained from all participants before commencement of the study. All investigations were conducted according to the principles expressed in the Declaration of Helsinki. The CONSORT checklist is provided as supporting information (see document, Supplemental Digital Content 1, CONSORT 2010 checklist of information related to original submission of this randomised trial, http://links.lww.com/MSS/B728).

#### **Study Participants**

The study recruited sedentary (<150 min of exercise per week), overweight (body mass index  $\ge 27 \text{ kg} \cdot \text{m}^{-2}$ ) men and

women between the ages of 18 and 65 yr. Participants were not eligible for this study if they were unable to exercise or had a condition known to be aggravated by exercise assessed using the Exercise and Sports Science Australia preexercise screening tool. In addition, participants were excluded if they (i) were using insulin; (ii) had undergone surgery for weight loss; (iii) had prior history of heart, lung, kidney, endocrine, or liver disease; and (vi) experienced recent weight loss  $\geq 4$  kg in previous month. Participants with T2D were allowed to continue their oral hypoglycemic medications at the usual dose, frequency, and time while participating in the study.

Using a medium effect size (f=0.25 [22]), a sample size of 34 participants was deemed sufficient to provide 80% power to detect ( $\alpha$ -error probability value set at 0.05) within–between interactions (two groups: amEX and pmEX) using measures taken at pre- and postintervention time points (G\*Power, version 3.0.10). To account for possible attrition, we increased the target sample size to 40 participants (see document, Supplemental Digital Content 2, Flowchart of participant recruitment, group assignment and study completion, http://links.lww.com/MSS/B729). Participants were recruited via public advertisements and enrolled between October 2016 and August 2017 and followed up until December 2017. The primary investigator of the study (ST) completed the recruitment of participants.

#### **Experimental Procedures**

At baseline, participants attended the Murdoch University Exercise Physiology laboratory after an overnight fast for their mixed meal tolerance test (MMTT). Before the start of the MMTT, venous blood sample was collected for the assessment of glycated hemoglobin (HbA<sub>1c</sub>), fasting glucose (FG), and insulin. Thereafter, frequent blood samples were obtained during the 4-h MMTT for the assessment of postprandial glucose (PPG) and insulin responses along with changes in postprandial area under the curve (AUC). During their subsequent visit, body anthropometrics were measured along with the assessment of peak oxygen consumption ( $\dot{VO}_{2peak}$ ). In addition, participants were then fitted with an accelerometer (ActiGraph) and a wrist skin temperature device (Thermochron iBotton DS1922L; Maxim Integrated Products, Inc., Sunnyvale, CA) for 7 d before commencement of the intervention (exercise program).

Upon completion of the baseline assessments, participants were assigned into either the amEX or the pmEX training groups. The allocation to the training groups was completed in a blinded fashion using a computer-generated numbered list consisting of 1s and 2s that represented the amEX and pmEX groups, respectively. Each participant was assigned with a unique study ID for identification and allocation purposes. This ID was forwarded to an investigator (TF; blinded to the identity of the participants) not involved in the training or assessments, who assigned each ID to a training group using randomly permutated blocks (each block n = 2-6; http://www.randomisation.com) with balanced treatment allocation ratio (i.e., 1:1). Males and females with and without T2D were counterbalanced across groups via generation of four separate lists (one for allocation

of T2D males, one for allocation of T2D females, one for allocation of non-T2D males, and one for allocation of non-T2D females). The final group allocation remained sealed in the envelope and revealed only before the first training session by an independent individual (KM; blinded to the recruitment process).

Midintervention  $\dot{VO}_{2peak}$  assessment was completed in week 6 to determine improvements in participant's fitness levels and to adjust the training workload accordingly. In weeks 12–13, participants completed their postintervention assessments, which were identical with the baseline assessments, at least 24 h after the last training session, but no more than 96 h after the last training session.

#### **Exercise Intervention**

All participants completed three supervised (by a trained exercise physiologist) exercise training sessions per week, for a total of 12 wk, at the Strength and Conditioning Laboratory in Murdoch University. Participants in both the amEX and the pmEX groups completed their training sessions between 0800-1000 h and 1700-1900 h, respectively. Participants were required to consume a snack/meal at least 1 h before the start of each training session. Each training session consisted of both an aerobic (AER) and a resistance (RE) exercise component, with an approximate session duration of 60 min. Each training session started off with the AER, which consisted of 30 min of treadmill walking at 60%–70% of  $\dot{V}O_{2peak}.$  This intensity was prescribed in accordance to the American Heart Association scientific statement (23). Thereafter, participants performed four different RE involving the major muscle groups (i.e., leg press, bench press, military press, and lateral pulldown). Three sets of each exercise were performed at 45%, 50%, and 55% of individually tested one-repetition maximums (1RM) for 18, 15, and 12 repetitions, with 60 s of rest between sets during weeks 1-4, 5-8, and 9-12, respectively. These training intensities were shown to be effective in improving glycemic control with no adverse events being reported other than mild muscle soreness in obese and/or elderly diabetic patients (24). Before the commencement of the training intervention, the 1RM for each participant had to be determined. The exercises in the 1RM test were completed in the following order: leg press, bench press, lateral pulldown, and military press. Two warm-up sets (first set, 10 repetitions; second set, 5 repetitions) were completed with 2 min rest in between sets. Thereafter, participants attempted their 1RM for each exercise with 3 min recovery between each sets and 5 min recovery between exercises.

**Outcome measures.** The primary outcome of this study was the change in glycemic control using  $HbA_{1c}$ . Changes in FG and PPG and insulin responses (PPG and postprandial insulin [PPI]) were assessed to identify their relative contribution and to help in the interpretation of  $HbA_{1c}$ . Secondary outcome measures included insulin resistance (HOMA2-IR) and sensitivity (muscle and hepatic), fructosamine (to assess the short-term glycemic change), and peripheral skin temperature (as the marker of circadian rhythm). Assessors of outcome measures were blinded to the treatment allocations.

### MMTT Procedure

Participants were requested to refrain from any physical activity 24 h before the MMTT. After an overnight fast, participants arrived at the Murdoch University Exercise Physiology laboratory between 7:00 AM and 7:30 AM. Upon arrival, a venous catheter for was inserted into the forearm vein for frequent blood sampling. Thereafter, participants were given a 4-h meal challenge (meal 1 and meal 2). The standardized meals provided during the MMTT were liquid SUSTAGEN® Diabetic beverages (1057 kJ; 52% carbohydrate, 22% fat, and 24% protein) containing 24.5 g of carbohydrate. Blood samples were collected for meal 1 (0, 15, 30, 45, 60, 90, and 120 min) and meal 2 (130, 145, 160, 175, 190, 210, and 240 min) for plasma glucose and insulin measurements (see Figure, Supplemental Digital Content 3, Schedule for timing of meals and blood sampling during each study visit, http://links.lww.com/MSS/ B730). All blood samples were transferred immediately into EDTA tubes, before being separated by centrifugation at 1300 RCF (relative centrifugal force) for 10 min. Thereafter, plasma were stored and frozen at -80°C until analysis.

**Biochemical analyses.** Glycated hemoglobin (HbA<sub>1c</sub>) was measured by an independent commercial pathology laboratory (Western Diagnostic Pathology, Perth, Western Australia), whereas plasma glucose (FG and PPG) and fructosamine (FRA; unadjusted for serum albumin) were measured using a COBAS analyzer (COBAS Integra 400 plus; Roche Diagnostics Ltd., Switzerland). Plasma insulin was measured using enzyme linked immunoassay (Mercodia, Uppsala, Sweden). The computerized homeostatic model assessment (HOMA2-IR) was used as a surrogate measure of insulin resistance based on FG and insulin concentrations (25). In addition, surrogate markers of muscle and liver insulin sensitivity were adopted using glucose and insulin concentrations (26). Muscle insulin sensitivity was calculated according to the slope (dG/dt) represented by the line of the least square fit from the peak to nadir glucose concentration, divided by the mean plasma insulin concentration (herein calculated as insulin-AUC / time). Hepatic insulin sensitivity was calculated according to the glucose<sub>0-30</sub>AUC multiplied by the insulin $_{0-30}$ AUC.

Body anthropometric and maximal oxygen consumption assessments. Body mass was calculated using a calibrated electronic digital scale, and body composition was measured using dual-energy x-ray absorptiometry to assess total body fat mass and fat-free mass. Cardiorespiratory fitness ( $\dot{VO}_{2peak}$ ) was measured during a modified Bruce treadmill test protocol by breath-by-breath analysis of oxygen consumption and carbon dioxide production (ParvoMedics TrueOne 2400). Rating of perceived exertion and heart rate were recorded throughout the test. The treadmill test protocol started at a speed of  $3.5 \text{ km}\cdot\text{h}^{-1}$  at 0% incline, with the speed progressively increasing by 1 km·h<sup>-1</sup> every 2 min. Once a speed of  $6.5 \text{ km}\cdot\text{h}^{-1}$  was achieved, incline was increased by 2% every 2 min while the speed was maintained at  $6.5 \text{ km}\cdot\text{h}^{-1}$  throughout these stages.

**Peripheral skin temperature.** Wrist skin temperature was continuously recorded (Thermochron iBotton DS1922L) for 7 d preintervention (before exercise training starting) and

at the postintervention time point (>24 h after the final training session). The use of iButtons for human skin temperature measurement has been previously reviewed (18) and shown to have an accuracy of  $-0.09^{\circ}$ C with a precision of  $0.05^{\circ}$ C. For this study, the iButton resolution was set at  $0.0625^{\circ}$ C, with sampling every 15 min, and the real-time clock synchronized with that of the computer.

Missing data and recording artifacts (recordings of skin temperature under 28°C) from the iButton were excluded from the analysis (less than 3% of the readings). The data from each participant collected across the 7 d of recording at the preintervention period, and the postintervention period were then analyzed for four rhythmic parameters: (i) MESOR (circadian rhythm adjusted mean temperature based on the parameters of a cosine function), (ii) amplitude (the difference between the temperature peak and the temperature MESOR of a cosine function), (iii) acrophase (the point at which the circadian temperature peak occurred), and (iv) the duration of each circadian cycle. The parameters were analyzed using the Cosinor software (available at http://www.circadian.org/ softwar.html). All data are presented relative to local time to minimize possible errors from the sleep-onset data recorded from the ActiGraph.

#### **Statistical Analyses**

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 24; IBM, Chicago, IL). Treatment effects were estimated using linear mixed models to assess for any changes over time (pre- and postintervention) in the primary and secondary outcome measures between the two intervention groups (amEX and pmEX). The primary hypothesis of interest was the group-time interaction, which were modeled as fixed effects with a random intercept (to account for differences at baseline), and these were examined with pairwise comparisons of the estimated marginal means. Because this trial included only active comparators (i.e., amEX and pmEX), main effects for time were also of interest and these were examined using pairwise comparisons of the estimated marginal means. Pearson bivariate correlations and hierarchical (two-step) linear regression models adopting both forced and stepwise methods of entry were used to explore associations of interest. Statistical significance was set at P < 0.05. The magnitude of change for each outcome measure was reported using Hedge's g and interpreted as small (g = 0.2), moderate (g = 0.5), or large (g = 0.8) (22). Data are presented as means  $\pm$  SD.

## RESULTS

Forty adults with (n = 20) or without T2D (n = 20) diagnosis completed the study (see document, Supplemental Digital Content 2, Flowchart of participant recruitment, group assignment and study completion, http://links.lww.com/MSS/B729). Twenty adults were allocated to the amEX group (female, n = 11; T2D, n = 10) and the pmEX group (female, n = 12; T2D, n = 10). With the exception of age (amEX,  $57 \pm 5$  yr; pmEX,  $51 \pm 13$  yr; P = 0.04), there were no significant differences at baseline in body mass index (amEX,  $31.2 \pm 3.8 \text{ kg}\cdot\text{m}^{-2}$ ; pmEX,  $30.9 \pm 4.2 \text{ kg}\cdot\text{m}^{-2}$ ), total body fat mass (amEX,  $27.3 \pm 7.9 \text{ kg}$ ; pmEX,  $28.8 \pm 7.4 \text{ kg}$ ), fat-free mass (amEX,  $56.9 \pm 12.0 \text{ kg}$ ; pmEX,  $55.2 \pm 9.5 \text{ kg}$ ), or  $\dot{\text{VO}}_{2\text{peak}}$  (amEX,  $22.5 \pm 6.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; pmEX,  $22.8 \pm 4.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) between groups (all  $P \ge 0.32$ ). The subcohort of individuals with T2D had similar patterns of disease duration (amEX,  $13 \pm 1 \text{ yr}$ ; pmEX,  $13 \pm 2 \text{ yr}$ ). Adherence rates between amEX ( $32 \pm 2$ ) and pmEX ( $31 \pm 2$ ) were similar during the 12-wk training intervention (total 36 sessions).

**Changes in glycemic control and insulin sensitivity.** Exercise training improved (main effect of time, all P < 0.01) glycemic control (HbA<sub>1c</sub>; fructosamine), FG, and insulin sensitivity (HOMA2-IR) in the overall cohort (n = 40; Table 1). However, allocation to the pmEX group conveyed no statistical improvement in glycemic control or insulin sensitivity versus allocation to the amEX group (all  $P \ge 0.42$ ). The calculated effect sizes of exercise training on glycemic control, FG, and insulin sensitivity ranged from 0.23 to 0.9 in the amEX group and from 0.16 to 0.9 in the pmEX group (Table 1).

In the subcohort of individuals diagnosed with T2D, exercise training significantly improved HbA1c, FG, and HOMA2-IR (main effect of time, all P < 0.01; Table 1), but not fructosamine (P = 0.09). However, there were no statistical benefits in glycemic control or insulin sensitivity when allocated to the pmEX group versus the amEX group (all  $P \ge 0.10$ ; Table 1). The calculated effect of exercise (pre- to postintervention) on glycemic control and insulin sensitivity ranged from 0.18 to 0.91 in the amEX group and ranged from 0.32 to 1.06 in the pmEX group (Table 1). The pattern of change in glycemia and the insulin sensitivity in the subcohort of individuals without T2D were similar to individuals with T2D (see Table, Supplemental Digital Content 4, Changes in glycemic control and insulin sensitivity from baseline to post-intervention for non-T2D individuals, http://links.lww.com/MSS/B731), except HbA1c, which demonstrated only small improvements (amEX, g = 0.18; pmEX, g = 0.10; main effect of time P = 0.03). Individual changes, stratified by training group and T2D status, in outcome measures (HbA<sub>1c</sub>, FG, FI, and HOMA-IR) are presented in Figure 1.

Changes in PPG and insulin responses. PPG and insulin responses are presented in Figure 2 and Table 2. Overall, significant reductions in PPG (main effect of time, all P < 0.01) and PPI (all  $P \le 0.02$ ) concentrations were observed after the training intervention. Moderate effects (Table 2) were observed in the maximum PPG response and total (4-h) AUC for both the amEX group (maximum PPG, g = 0.47; 4-h AUC, g = 0.46) and the pmEX group (maximum PPG, g = 0.39; 4-h AUC, g = 0.43). These effects were moderate-large when only the T2D cohort was assessed (amEX, g = 0.62, g = 0.51; pmEX, g = 0.75, g = 0.71; maximum PPG and 4-h AUC, respectively). Allocation to the pmEX group conveyed no additional advantage in any PPG response measures (all  $P \ge 0.13$ ). The magnitude of effect across all reported insulin variables ranged from g = 0.35 to g = 0.76 for both amEX and pmEX training groups. The variable of interest, insulin-AUC, demonstrated moderate to large effects in both the amEX group

TABLE 1.	Changes in (	alvcemic co	ntrol and insuli	n sensitivity f	rom baseline to	postintervention	for non-T2D and	T2D individuals.
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		Overall ( <i>n</i> = 40)						T2D ( <i>n</i> = 20)					
					Р					Р			
		amEX ( <i>n</i> = 20)	pmEX ( <i>n</i> = 20)	Group–Time Effect	Time Effect	Group Effect	amEX ( <i>n</i> = 10)	pmEX ( <i>n</i> = 10)	Group–Time Effect	Time Effect	Group Effect		
HbA <sub>1c</sub> (%)	Week 0	6.85 ± 1.23	6.79 ± 1.66				7.91 ± 0.74	8.04 ± 1.44					
	Week 12	6.58 ± 1.1	6.54 ± 1.46				7.34 ± 0.81	7.64 ± 1.35					
	Change	-0.27 ± 0.24	-0.25 ± 0.23				-0.57 ± 0.13	-0.4 ± 0.12					
	ES	0.23	0.16	0.79	<0.01*	0.90	0.57	0.32	0.86	<0.01*	0.79		
FG (mmol·L <sup>-1</sup> )	Week 0	7.68 ± 1.70	8.28 ± 3.72				9.02 ± 1.33	10.32 ± 4.33					
	Week 12	6.78 ± 1.45	7.10 ± 2.41				7.76 ± 1.33	8.52 ± 2.69					
	Change	-0.9 ± 0.68	-1.18 ± 1.40				-1.27 ± 0.75	-1.80 ± 1.77					
	ES	0.56	0.37	0.42	<0.01*	0.55	0.91	0.53	0.39	<0.01*	0.39		
Fasting insulin (pmol·L <sup>-1</sup> )	Week 0	88.3 ± 33.9	81.0 ± 29.7				81.7 ± 27.9	85.3 ± 24.6					
	Week 12	64.4 ± 23.4	58.6 ± 22.1				62.6 ± 21.5	64.4 ± 18.9					
	Change	-23.9 ± 27.8	-22.3 ± 22.7				-19.2 ± 17.8	-20.8 ± 17.2					
	ES	0.8	0.83	0.85	<0.01*	0.40	0.74	1.06	0.83	<0.01*	0.79		
HOMA2-IR	Week 0	1.78 ± 0.66	1.70 ± 0.71				1.74 ± 0.57	1.94 ± 0.70					
	Week 12	1.26 ± 0.46	1.16 ± 0.45				1.28 ± 0.44	1.35 ± 0.40					
	Change	-0.52 ± 0.53	-0.54 ± 0.48				-0.46 ± 0.36	-0.59 ± 0.46					
	ES	0.9	0.9	0.92	<0.01*	0.58	0.18	0.99	0.49	<0.01*	0.54		
Fructosamine (µmol·L <sup>-1</sup> )	Week 0	262.5 ± 45.2	259.8 ± 53.6				286.5 ± 44.6	287.9 ± 57.7					
	Week 12	227.9 ± 77.8	230.2 ± 61.9				235.2 ± 108.5	267.9 ± 65.4					
	Change	-34.5 ± 78.9	-29.6 ± 51.2				-51.3 ± 107.9	-20 ± 61.6					
	ES	0.53	0.5	0.70	<0.01*	0.99	0.61	0.32	0.10	0.09	0.50		

Data are presented as mean ± SD.

\*Significant difference between baseline and postintervention (P < 0.05).

Overall, combined results of non-T2D and T2D individuals; T2D, only results of T2D individuals; amEX, morning exercise group; pmEX, evening exercise group; HbA<sub>1c</sub>, glycosylated hemoglobin; HOMA2-IR, homeostatic model of insulin resistance; ES, effect size (Hedge's g).

(overall cohort, g = 0.76; T2D cohort, g = 0.87) and the pmEX group (overall cohort, g = 0.63; T2D cohort, g = 0.60). Allocation to the pmEX group conveyed no statistical improvement in any PPI response measures (all  $P \ge 0.84$ ).

There were no significant benefits to allocation to either group with respect to the surrogate markers of insulin sensitivity (muscle or hepatic insulin sensitivity, all  $P \ge 0.49$ ; data not reported). Consistent with the glucose and insulin data, hepatic insulin sensitivity improved after the exercise training in the overall cohort (amEX, g = 1.05; pmEX, g = 0.82), individuals with T2D (amEX, g = 1.35; pmEX, g = 1.16), and individuals without T2D (amEX, g = 0.80; pmEX, g = 0.57) (all  $P \le 0.01$ ). There were no improvements observed in muscle insulin sensitivity in any groups (all  $P \ge 0.14$ ).

The iAUC response to meal 2 (196.6 ± 143.2 mmol·L<sup>-1</sup> per 120 min) was smaller (P < 0.01) than meal 1 (240.3 ± 150.4 mmol·L<sup>-1</sup> per 120 min) at baseline in the overall cohort (Fig. 2 and Table 2), and this persisted posttraining (meal 1, 227.5 ± 115.6 mmol·L<sup>-1</sup> per 120 min; meal 2, 156.3 ± 92.3 mmol·L<sup>-1</sup> per 120 min;  $P \le 0.01$ ). This was consistent in both T2D (meal 1, 226.8 ± 113.4 mmol·L<sup>-1</sup> per 120 min; meal 2, 162.5 ± 96.3 mmol·L<sup>-1</sup> per 120 min;  $P \le 0.01$ ) and non-T2D (meal 1, 228.3 ± 117.8 mmol·L<sup>-1</sup> per 120 min; meal 2, 156.3 ± 87.5 mmol·L<sup>-1</sup> per 120 min;  $P \le 0.01$ ) cohorts (see Table,



FIGURE 1—Individual changes from baseline to postintervention (T2D, *dashed lines*; non-T2D, *solid lines*) in HbA<sub>1c</sub>, FG, fasting insulin, and insulin resistance after amEX and pmEX training.



FIGURE 2—Postprandial changes in glucose (A; top four panels) and insulin (B; bottom four panels) in response to the two meals (M1 and M2). Time (min) is indicated on the *x*-axis. *Open circles* represent the preintervention means, and *solid black squares* represent the postintervention means. Error bars represent the SD.

Supplemental Digital Content 5, Incremental changes in postprandial glucose and insulin from baseline to postintervention for the overall cohort and T2DM only, http://links.lww.com/ MSS/B732; see Table, Supplemental Digital Content 6, Changes in postprandial glucose and insulin responses as well as incremental changes from baseline to post-intervention for non-T2D individuals, http://links.lww.com/MSS/B733).

Associations between markers of glycemia and insulin sensitivity. Significant correlations (all n = 80; pre- and posttraining) between HbA<sub>1c</sub> and FG (r = 0.74), 4-h glucose-AUC

			Overa		T2D ( <i>n</i> = 20)						
					Р					Р	
		amEX ( <i>n</i> = 20)	pmEX ( <i>n</i> = 20)	Time Effect	Group Effect	Group–Time Interaction	amEX ( <i>n</i> = 10)	pmEX ( <i>n</i> = 10)	Time Effect	Group Effect	Group–Time Interaction
Maximum PPG (mmol·L <sup>-1</sup> )	Week 0 Week 12 Change	10.74 ± 2.66 9.58 ± 2.21 -1.16 ± 1.36	11.35 ± 4.63 9.69 ± 3.56 -1.66 ± 1.44				13.07 ± 1.48 11.2 ± 0.86 -1.87 ± 1.17	14.81 ± 3.41 12.44 ± 2.55 -2.37 ± 2.27			
4-h PPG-AUC (mmol·L <sup>-1</sup> ·min <sup>-1</sup> )	ES Week 0 Week 12 Change	0.45 9.41 ± 2.35 8.39 ± 1.95 -1.02 ± 0.98	0.39 10.12 ± 4.21 8.5 ± 3.17 -1.62 ± 1.52	<0.01*	0.72	0.36	0.26 11.31 ± 1.46 9.9 ± 0.85 -1.41 ± 1.05	0.7 $13.3 \pm 3.77$ $10.8 \pm 2.89$ $-2.5 \pm 1.68$ 0.71	<0.01*	0.22	0.56
2-h PPG-AUC Meal 1 (mmol·L <sup>-1</sup> ·min <sup>-1</sup> )	ES Week 0 Week 12 Change ES	0.46 10.04 ± 2.51 8.98 ± 2.13 -1.06 ± 1.1 0.45	0.43 10.68 ± 4.53 9.15 ± 3.38 -1.53 ± 1.63 0.38	<0.01	0.00	0.15	12.12 ± 1.42 10.61 ± 0.91 -1.51 ± 0.90 1 2	0.71 14.1 ± 4.08 11.65 ± 2.99 -2.45 ± 1.87 0.65	<0.01	0.22	0.11
Meal 2 (mmol·L <sup>-1</sup> ·min <sup>-1</sup> )	Week 0 Week 12 Change ES	9.49 ± 2.43 8.43 ± 1.95 -1.06 ± 1.02 0.47	10.33 ± 4.26 8.48 ± 3.21 -1.85 ± 1.57 0.48	<0.01*	0.65	0.02	11.38 ± 1.73 9.95 ± 1.06 -1.43 ± 1.19 0.98	13.55 ± 3.83 10.79 ± 1.51 -2.76 ± 1.73 0.78	<0.01*	0.22	0.07
Maximum PPI (pmol·L <sup>-1</sup> )	Week 0 Week 12 Change	501 ± 240 371 ± 146 -130 ± 157	432 ± 269 309 ± 165 -123 ± 206	0.044		0.00	501 ± 249 342 ± 152 -159 ± 117	409 ± 305 268 ± 132 -141 ± 296	0.011	0.07	0.00
4-h PPI-AUC (pmol·L <sup>−1</sup> ·min <sup>−1</sup> )	ES Week 0 Week 12 Change	0.62 230.23 ± 104.8 165.66 ± 54.65 -64.57 ± 75.65	0.53 199.75 ± 109.38 133.23 ± 97.14 -66.52 ± 28.91	<0.01*	0.3	0.92	0.5 227.82 ± 92.45 157.81 ± 57.2 -70.01 ± 45.22	0.22 201.21 ± 124.18 125.65 ± 115.38 -75.56 ± 29.83	<0.01	0.37	U.ŏb
	ES	0.76	0.63	<0.01*	0.3	0.92	0.87	0.6	<0.01*	0.22	0.76

Data are presented as mean ± SD.

\*Significant difference between baseline and postintervention (P < 0.05).

Overall, combined results of non-T2D and T2D individuals; T2D, only results of T2D individuals; amEX, morning exercise group; pmEX, evening exercise group; PPI, postprandial insulin; AUC, area under the curve (values above absolute zero); ES, effect size (Hedge's g).

(r = 0.84), iAUC (r = 0.55), fructosamine ( $r_p = 0.511$ ), and HOMA2-IR ( $r_p = 0.346$ ) were observed. Regression modeling revealed the best predictor of HbA<sub>1c</sub> was the 4-h glucose-AUC value (model adjusted  $r^2 = 0.71$ ). The 2-h glucose-AUC from meal 1 (r = 0.85) and meal 2 (r = 0.82) demonstrated similar correlations with HbA<sub>1c</sub> as compared with the 4-h glucose-AUC. Improvements in HbA<sub>1c</sub> (all n = 40; pretraining subtract posttraining) were associated with improvements in the 4 h glucose-AUC (r = 0.47) and FG (r = 0.47).

Secondary analysis: assessing glycemic changes in "responders" and "nonresponders." To assess whether individuals demonstrating the greatest response to training were also those demonstrating the greatest improvements in glycemic control, data from all individuals were collapsed across groups (amEX T2D and non-T2D; pmEX T2D and non-T2D) and compared using an independent-samples *t*-test. Response to training was based on an increase in  $\dot{VO}_{2peak}$  above 3.5 mL·kg<sup>-1</sup>·min<sup>-1</sup> (Fig. 3A) and a decrease in total body fat (kg;  $\geq 2.1$  kg body fat; Fig. 3B). Although responders tended to demonstrate more consistent improvements for measures of glycemic control, insulin sensitivity, and changes in PPG and insulin responses ( $\dot{VO}_{2peak}$  responders: g = 0.18-1.16, n = 23 [T2D, n = 10]; total body fat responders: g = 0.16-0.67, n = 24 [T2D, n = 15]), these did not reach statistical significance (all  $P \geq 0.15$ ; Fig. 3).

**Peripheral skin temperature responses.** There were no significant differences observed with the exercise training intervention in any of the rhythmic parameters assessed in the overall cohort (all  $P \ge 0.35$ ; Fig. 3). Peripheral skin temperature

data were graphed (Fig. 4), and the effect of training was directly compared by subtracting the postintervention data from the preintervention data for each participant (bottom two panels, Fig. 4). The 95% confidence intervals were then calculated for each group (amEX, left; pmEX, right). If these intervals cross the zero line, it was interpreted as indicating a difference. A divergent response in peripheral skin temperature to the exercise intervention appeared to occur around the late-morning period (amEX, minor elevation; pmEX, minor depression); however, statistical analysis did not confirm this observation in the overall cohort. The pattern of change in the rhythmic parameters was similar in the T2D cohort as they were in the overall cohort, with the exception that the amEX cohort had a significantly greater shift in the acrophase parameter (Fig. 4).

The rhythmic parameters at the preintervention time point were compared between individuals with and without T2D. There were no significant differences between these groups (T2D; non-T2D) in the MESOR (non-T2D, 33.56°C ± 0.79°C; T2D, 33.65°C ± 0.78°C; P = 0.71), amplitude (non-T2D, 0.93°C ± 0.55°C; T2D, 1.06°C ± 0.40°C; P = 0.36), or acrophase (non-T2D,  $-112.65 \pm 112.72$ ; T2D,  $-82.6 \pm 64.86$ ; P = 0.32).

#### DISCUSSION

This study sought to determine whether the diurnal timing of a multimodal exercise training program influences glycemic responses in previously sedentary, overweight individuals with and without T2D. The main findings were (i) 12 wk of



FIGURE 3—Individuals changes in body anthropometrics (A) and  $\dot{VO}_{2peak}$  (B) for the overall cohort from baseline to postintervention. Change in HbA<sub>1c</sub>, FG, fructosamine, HOMA2-IR, 4-h PPG-AUC, and 4-h PPI-AUC responses between responders (black column) and nonresponders (gray column) are compared below. *p* represents the *P* value from the independent Student *t*-test; *g* represents the Hedge's *g* effect size for each comparison.

multimodal exercise training in overweight T2D and non-T2D individuals resulted in significant improvements in measures of glycemic control (HbA1c), glycemia (FG), and PPG (glucose-AUC) responses; (ii) under the adopted free-living conditions, and contrary to our hypothesis, there were no benefits to performing the exercise in the evening relative to the morning in any of the outcomes assessed in the study; and (iii) when comparing only individuals with T2D, exercise training in the morning appeared to elicit larger improvements in glycemic outcomes; however, further research with a greater number of participants with T2D is required to confirm this observation. A secondary aim of this study was to determine the effect of morning and evening exercise on the circadian rhythm of peripheral skin temperature. Over a 12-wk period, 3 d of exercise performed either in the evening or in the morning was not sufficient to changes the circadian rhythm of wrist temperature. Overall, significant improvements in glycemic outcomes were identified; however, improvements were independent of the diurnal timing of exercise and appeared not to be associated with changes in the circadian rhythm of body temperature.

Effect of exercise timing on glycemic control and insulin sensitivity. In response to the 12-wk exercise intervention, statistically significant improvements in FG ( $-1.04 \text{ mmol}\cdot\text{L}^{-1}$ ) and HbA<sub>1c</sub> (-0.26%) were observed, but there were no significant group–time interactions (Table 1). This finding suggests that under free-living conditions with no additional behavioral modifications (e.g., diet), exercise performed three times per week in a short-to medium-term training period (12 wk) is sufficient to improve glycemic control. However, the diurnal timing of exercise does not appear to be an important consideration under the current conditions.

These findings in the overall cohort were reflected in the T2D cohort, albeit these improvements in individuals with T2D were considerably greater (FG,  $-1.54 \text{ mmol}\cdot\text{L}^{-1}$ ; HbA<sub>1c</sub>, -0.45%). These improvements in HbA<sub>1c</sub> are in agreement with previous findings from meta-analyses in individuals with T2D (mean-weighted decrease in HbA1c from 0.66% to 0.80% [27,28]) and a longer-term (9-month) randomized controlled exercise intervention (within-group HbA<sub>1c</sub> change, -0.23% [27]). Interestingly, the greatest within-group benefits in HbA<sub>1c</sub> (~0.29%reduction) for individuals randomized to the combination exercise group in the study by Church et al. (27) were observed at the 12- to 16-wk training period, which coincides with the 12-wk intervention adopted herein. With respect to the clinical findings in the current study, it is noteworthy that eight individuals with T2D achieved the <7% HbA<sub>1c</sub> recommendation (28) (preintervention, 2/20 individuals achieved recommendation; postintervention, 10/18 individuals achieved recommendation), with five individuals from the amEX and three individuals from the pmEX achieving this recommendation.

Two additional markers of glycemia were included in the current study, HOMA2-IR and fructosamine. Fructosamine is a short-term (1–3 wk), nonspecific marker of glycation, thereby complementing HbA<sub>1c</sub> values in short- to medium-term intervention trials (29). Exercise training resulted in a significant improvement in fructosamine levels, with the magnitude of improvement being similar between morning and evening exercise groups (Hedge's *g* effect range, 0.32–0.61). Insulin sensitivity was assessed via the HOMA2-IR (23,25) and revealed significant improvement in the overall cohort largely reflects changes in insulin concentration rather than glucose concentration.



FIGURE 4—Changes in circadian rhythm parameters (table) and peripheral skin temperature from pre- to postexercise training. Group mean data are presented in the top panels with difference (95% confidence intervals presented in the bottom two panels). Data are presented relative to the time of day (local time).

Effect of exercise timing on PPG and insulin responses. The postprandial decrease in glucose concentrations after exercise training was 2.0 and 0.7 mmol·L<sup>-1</sup>·min<sup>-1</sup> over the 4-h study period in individuals with T2D and without T2D, respectively. Improvements in insulin (4-h AUC g = 0.60 - 0.87) were greater than those observed with glucose (4-h AUC g = 0.43-0.71), wherein insulin concentrations were reduced by 100.1 and 98.2  $\text{pmol}\cdot\text{L}^{-1}$  over the 4-h study period in individuals with and without T2D, respectively. The similar insulin responses to exercise training in individuals with T2D and without T2D suggest both a level of insulin resistance in individuals without T2D in this cohort and highlights the continued responsiveness in those with T2D. The changes in the surrogate measures of insulin sensitivity adopted herein suggest that hepatic insulin sensitivity was significantly improved in response to training in both the non-T2D and the T2D cohorts, and this occurred independent of the timing of exercise. However, there was no change in muscle insulin sensitivity according to the adopted measure, which was surprising given we anticipated a greater change in muscle insulin sensitivity than hepatic insulin sensitivity. A possible explanation may relate to the intensity of exercise not being sufficient to stimulate the necessary metabolic or molecular changes required to upregulate insulin sensitivity despite the exercise intensity meeting current guidelines (28). The significant postprandial benefits associated with the exercise training program occurred independent of the timing of exercise. The lack of effect associated with the exercise timing is contrary to our hypothesis; however, this hypothesis was underpinned by proposed changes in

the circadian rhythm, which was not observed (as measured by peripheral temperature) in the current study.

Correlations between HbA<sub>1c</sub> with PPG (r = 0.68) and FG (r = 0.61) have previously been reviewed (30). These correlations, however, are moderated by glycemic control (i.e., HbA<sub>1c</sub> levels) with stronger correlations between PPG and HbA<sub>1c</sub> when individuals achieve good control (HbA<sub>1c</sub> < 7.3%) (31). This supports observations in our cohort (HbA<sub>1c</sub> levels ~6.8%), wherein the 4-h glucose-AUC had a stronger correlation with HbA<sub>1c</sub> (r = 0.84). In contrast to our stated hypothesis, the improvements in FG (r = 0.46) and the glucose-AUC (r = 0.47). The strong association between HbA<sub>1c</sub> and PPG-AUC supports the importance of considering both FG and PPG in individuals with T2D and individuals at risk of developing T2D (32).

It is noteworthy that within the T2D cohort, improvements in FG and PPG (4-h glucose-AUC) were greater in response to amEX training than in the pmEX group (based on effect size), and this culminated in greater changes in HbA<sub>1c</sub>. These are the components of the glucose triad (HbA<sub>1c</sub>, FG, and PPG [33]). Glucose tolerance deteriorates to a greater extent in the morning in individuals with T2D, such that tolerance in the morning and evening is no longer different as they are in normoglycemic individuals (12). This is likely associated with the sudden rise in glucose concentration in the early morning associated with the "dawn phenomenon" (34). This dawn phenomenon is associated with complex changes in the metabolic and endocrine milieu. Although speculative, consistent morning exercise may blunt this phenomenon and reduce the

waking (fasted) glucose concentration as well as the morning-PPG response; although to the best of our knowledge, this has not been assessed.

Effect of exercise timing on PPG: second meal phenomenon. The disrupted circadian pattern in glucose tolerance (11) along with the early morning glucose spike (i.e., dawn phenomenon) has long been acknowledged in individuals with T2D (32). Superimposed on this circadian glucose pattern is the second meal phenomenon, which is presumed to be associated with changes in the gastric emptying rate (i.e., slowed after the first meal) or an altered plasma metabolite/endocrine milieu after the previous meal (35). In accordance with expectations of the second meal phenomenon, and despite the relatively short interval between eating occasions, the glucose response to the second meal (glucose-AUC) was significantly blunted in the current study. Although acute exercise has been shown to alter the second meal response (36), the findings of the current study are that this response appears to remain unaffected (relative to the first PPG meal response) after a 12-wk exercise training program. The second meal phenomenon was observed in both the overall and the T2D cohorts herein and was preserved posttraining with no apparent effect of exercise timing (morning vs evening) on this response.

Secondary analysis: assessing glycemic changes in "responders" and "nonresponders." The overall cohort was divided into responders and nonresponders to the exercise program according to their improvements in  $\dot{VO}_{2peak}$ and total body fat mass. The 3.5-mL·kg<sup>-1</sup>·min<sup>-1</sup> cut point was based on the associated 10%–25% reduction in mortality risk for every 1 MET (3.5 mL·kg<sup>-1</sup>·min<sup>-1</sup>) increase in exercise capacity (37). The cut point (–2.1 kg) to identify responders and nonresponders for total fat mass over 12 wk was calculated using the following assumptions: ~600 kcal were expended per session, and ratio of fat loss and muscle loss was 70:30. These assumptions result in an approximate 250-g weight loss (175-g fat loss) per week. Direct comparison of these groups demonstrates favorable glycemic improvements in responders versus nonresponders, but these were not significantly different.

Effect of exercise timing on circadian rhythm of skin temperature. Changes in the circadian rhythm of skin temperature were assessed in response to the exercise intervention, with the hypothesis that the morning and evening exercise would result in divergent responses in the circadian rhythm of wrist skin temperature. Although a circadian rhythm in skin temperature was evident, the rhythm parameters assessed (MESOR, Amplitude, Acrophase) did not demonstrate a significant interaction effect (all  $P \ge 0.43$ ) or a main effect of time (all  $P \ge 0.35$ ). Therefore, the three supervised exercise sessions of moderate-intensity adopted in isolation (i.e., no other lifestyle intervention) in this study were insufficient to significantly change the circadian rhythm parameters as assessed by the cosinor function of wrist skin temperature collected over 7 d. It may be plausible that higher-intensity exercise or a greater duration of exercise may result in a more pronounced shift in the circadian rhythm, given that circulating metabolites may alter cellular clocks (and vice versa [13,16]) and greater

intensity is expected to yield greater shifts in metabolites. However, it is more likely that consistency in exercise performance (i.e., increased frequency from 3 sessions per week) at a set diurnal time more likely leads to circadian entrainment. This is an area that requires further work. Further analysis comparing individuals with T2D and without T2D did not reveal significant differences in the circadian parameters, despite prior research suggesting reduced amplitudes and elevated MESOR in the circadian rhythm of body temperature (measured via thermometer) in T2D individuals versus individuals with prediabetes (19). In individuals with metabolic syndrome, however, reduction in the amplitude of the circadian rhythm of wrist skin temperature was revealed to be associated more strongly with triglycerides (20), which explained 33% of the variability in amplitude. Unfortunately, the current study did not measure triglyceride concentrations.

Strengths and limitations. The main strength of the study was implementation of a structured, supervised exercise training program comprising up to approximately 180 min  $\cdot$  wk<sup>-1</sup> of exercise in individuals with T2D or at risk of developing T2D, along with the adoption of a 4-h study period comprising two separate mixed meals. The multicomponent (resistance training and aerobic training) exercise training program is associated with the greatest glycemic benefits (27), adheres with current guidelines (3), and allows modification of the frequency, intensity, type, and time (FITT) principle to ensure individualization (38). Research has shown that structured exercise durations of >150 min allowed for greater reductions in HbA<sub>1c</sub> when compared with durations of  $\leq 150 \min(-0.80\% \text{ vs} - 0.36\%, \text{ re-}$ spectively) (39). An additional strength of the study was that every exercise session throughout the training program was supervised. There is evidence that exercise supervision results in improved glycemic control and insulin sensitivity, whereas unsupervised exercise leads to a decline in exercise compliance and glycemic control (40).

Although the study had a number of strengths, there were also limitations of the study. Inclusion of a nonactive control group along with tighter control of the diurnal timing of meal ingestion (beyond the postprandial exercise requirement) and incidental physical activity patterns between groups may have amplified the between-group difference observed. Although physical activity is known to entrain the circadian rhythm, dietary intake may also alter the circadian rhythm (15). To minimize potential confounders within the study (i.e., not introducing additional requirements), participants were asked to maintain their usual dietary habits; however, change in circadian rhythm may require a concerted focus of both diet and exercise during the awake phase. An increase in sample size would have allowed comparisons between subcohorts (i.e., four subgroups: pmEX OW, pmEX T2D, amEX OW, and amEX T2D) or to explore individual differences more thoroughly using advanced multiple linear regression analyses. There appeared to be a trend demonstrating greater effects of morning training (amEX) on HbA1c, FG, and fructosamine when only the T2D cohort was considered, whereas the pmEX group demonstrated greater PPG responses. Finally, the marker of circadian rhythm adopted

(wrist skin temperature) may not reflect the circadian rhythm of skeletal muscle cells or hepatocytes, which are the ultimate target of interventions designed for individuals with T2D.

## CONCLUSIONS

This study showed that 12 wk of multimodal exercise training without additional dietary restriction was effective in improving glycemic control, insulin sensitivity, and PPG responses to the ingestion of a mixed meal in overweight individuals with and without T2D. However, these improvements occurred independent of diurnal exercise timing (morning or evening). Accordingly, the adopted exercise training program in this study did not alter the circadian rhythm of skin temperature. Given the importance of exercise intensity (3) in increasing insulin sensitivity along with the greater effects of amEX on components of the glucose triad, as well as the likely importance of frequency in altering circadian patterns (41), it may be prudent for future research to increase the intensity and frequency of exercise to comprehensively exclude a

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role for diurnal timing of exercise in altering glycemic control. This is particular relevant when considering that exercise training in the morning appeared to elicit larger improvements in glycemic outcomes for individuals with T2D. The existing evidence supports the manipulation of exercise intensity, type, and volume (duration and frequency) of exercise to help manage glycemia in individuals with T2D (3,6); however, the findings from this study suggest that diurnal timing may not be an important factor to consider as part of this management plan.

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